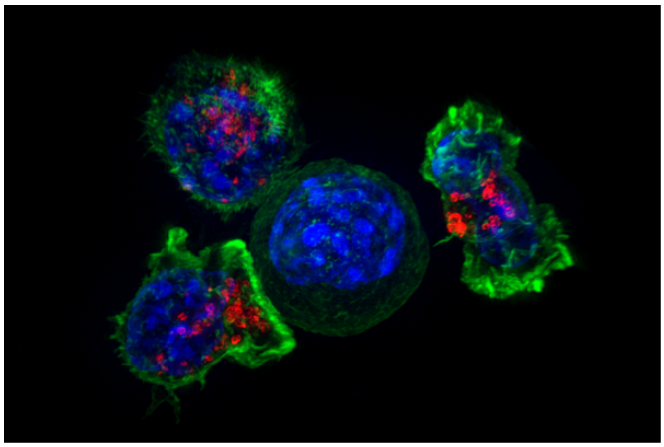
Research team discovers new target for CAR T cells in solid tumors

5 May 2022



Killer T cells surround a cancer cell. Credit: NIH

Chimeric antigen receptor T-cell therapy, or CAR T, has made a big impact on the treatment of certain blood cancers, allowing patients with relapsed/refractory disease to live longer, healthier lives. But in clinical study, the cellular therapy has not been as successful for patients with solid tumors, due in part to the lack of tumor targets not expressed in vital tissues. In a new study published in *Molecular Cancer Therapeutics*, a journal of the American Association for Cancer Research, Moffitt Cancer Center researchers share the identification of a new potential target for CAR T cells called OR2H1 that they have demonstrated inhibits growth in lung and ovarian tumors.

The key to CAR T-cell therapy is the genetic modification made to the patient's T cells. Their cells are collected through a process called apheresis, and then shipped to a laboratory where the cells are modified to contain a gene for the T cell receptor that recognizes a specific marker on cancer cells. Those modified T cells, now CAR T cells, are stimulated to grow and multiply before being sent back to the hospital to be infused back into the patients. The receptor on the CAR T cells acts as a GPS, seeking out their specific marker on the surface of the cancer cells. Currently there are CAR T therapies approved to treat patients with lymphoma, leukemia and multiple myeloma, but there are no approved CAR T therapies for solid tumors.

Moffitt researchers are working to identify tumor markers that can make CAR T an effective therapy for patient with solid tumors. The goal is to find a marker that is expressed on tumor cells but not on normal cells, to reduce the potential for unwanted toxicities. The team, led by Dr. Jose Conejo-Garcia, focused the search on a family of proteins called olfactory receptors that are expressed in the nose and contribute to the perception of smell. During lab experiments, they discovered that the protein OR2H1 is expressed in a variety of solid tumors, ranging from 4% of colon cancer samples to 69% of cancers of the gall bladder. Importantly, of all normal tissues examined, OR2H1 was found only in the testis, suggesting that therapies that target OR2H1 would have minimal effects on normal cells.

The researchers then created CAR T cells that were specific to the OR2H1 protein. The OR2H1 CAR T cells were able to kill lung and ovarian cancer cells that expressed OR2H1 but had no effect on healthy cells. The OR2H1 CAR T cells also had anti-tumor effects in vivo in immunodeficient mice challenged with human tumors. Tumor inhibition was observed in lung and ovarian cancer mice models with varying levels of OR2H1, including ovarian cancer cells that were resistant to chemotherapy.

These combined data suggest that OR2H1 may be an effective target for CAR T therapies in solid tumors. The researchers hope these initial studies will lead to the development of OR2H1 CAR T cells for a wide variety of patients with solid tumors.

"Our work demonstrates the applicability of this therapy to a wide variety of patients, given the

expression of OR2H1 in a subset of solid tumors across multiple histologies, including high-grade serous ovarian cancers, lung carcinoma, cholangiocarcinoma, prostate cancer and ovarian cancers of multiple other histologies. Targeting a molecule that is not expressed in vital tissues would allow us to further engineer T cells to overcome immunosuppression at tumor beds, if needed," said Conejo-Garcia, chair of Moffitt's Department of Immunology.

More information: Alexandra L. Martin et al, Olfactory Receptor OR2H1 is an effective target for CAR T cells in human epithelial tumors, *Molecular Cancer Therapeutics* (2022). DOI: 10.1158/1535-7163.MCT-21-0872

Provided by H. Lee Moffitt Cancer Center & Research Institute